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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,732	11/19/2001	Avi J. Ashkenazi	P2730P1C57	2430

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EXAMINER	
JIANG, DONG	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,732	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/24/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's preliminary amendment filed on 19 November 2001 is acknowledged and entered. Following the amendment, the original claims 1-118 are canceled, and the new claims 119-138 are added.

Currently, claims 119-138 are pending and under consideration.

Formal Matters:

Priority

This application claims priority to US provisional application 60/088,741, PCT/US99/12252, 60/141,037, 09/380,137, PCT/US00/05841, PCT/US00/08439, and 09/941,992. For the following reasons, the Examiner finds that the present claims 119-138 are not supported in the manner required by 35 U.S.C. 101 and 112, first paragraph by all of the prior applications, thus the present claims are not entitled to the benefit of the filling date of all of the prior applications.

The priority applications 60/088,741, PCT/US99/12252, 60/141,037, 09/380,137, PCT/US00/05841 merely disclose the nucleic acid sequence of SEQ ID NO:269, which encodes the PRO1184 polypeptide having SEQ ID NO:270, and fail to provide any specific and substantial utility for the claimed the nucleic acid or the polypeptide encoded thereby, and provides no guidance or working examples to teach how to used the claimed invention. Therefore, the Examiner is not able to establish that the priority documents 60/088,741, PCT/US99/12252, 60/141,037, 09/380,137, PCT/US00/05841 satisfy the utility/enablement requirement of 35 U.S.C. 101/112, first paragraph. As such, the claims of the instant application are not entitled to the benefit of the filling date of prior applications 60/088,741, PCT/US99/12252, 60/141,037, 09/380,137, PCT/US00/05841. Priority is granted to the filing date of the later application, PCT/US00/08439, filed on **30 March 2000**, in which some specific biological properties of said PRO1184 polypeptide were disclosed, such as inducing re-differentiation of chondrocytes (Example 159), which constitutes specific and substantial utility.

Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are directed.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 119-138 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 119-124, 127, 128, and 132 recite the "extracellular domain". However, the protein identified as PRO1184 is a secreted protein, and is not disclosed as being expressed on a cell surface. Accordingly, the limitation that the claimed protein comprises the "extracellular domain" is indefinite, as the art does not recognize soluble proteins as having such domains. Further, if the protein had an extracellular domain, the recitation of "the extracellular domain ..., lacking its associated signal sequence" (claim 119, part (d), for example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

Claim 133 is further indefinite because the claim is incomplete for omitting essential elements. The claim is limited by a hybridization method "under stringent conditions". The specification does not define such conditions. As the target sequence is specific, an artisan needs to know the specific corresponding hybridization conditions in order to practice the claimed invention. The claim recites neither hybridization conditions to ensure that any hybridized polynucleotides will comprise specific sequence within the meaning of the disclosure, nor process steps which would effect the removal of nonspecific hybridization complexes. Without knowing what conditions are comprised by "stringent" conditions, one cannot determine the metes and bounds of nucleic acids within the limitations of the claim.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-124, 127, 128, and 132-138 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a nucleic acid of SEQ ID NO:269, and a nucleic acid encoding a polypeptide of SEQ ID NO:270, does not reasonably provide enablement for claims to various variants and fragments of SEQ ID NO:269 or of a nucleotide sequence encoding SEQ ID NO:270, which do not have a functional activity, or do not have the same functional activity as SEQ ID NO:270, such as % variants (claims 119-123 and 135-138, for example), hybridization variants thereof under stringent conditions (claim 132 and 133, for example), fragments of hybridization variants (claim 134, for example), a fragment encoding the extracellular domain SEQ ID NO:270 (claims 119-124, 127 and 128, for example). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are directed to % variants, hybridization variants, fragments thereof, and fragments of the nucleic acid of SEQ ID NO:269, or of a nucleic acid encoding a polypeptide of SEQ ID NO:270, or the extracellular domain thereof, which read on any or all variants meeting the sequence limitation, and encoding polypeptides either with or without a functional activity. The claims encompass an unreasonable number of nucleic acids encoding inoperative polypeptides. However, while the specification teaches that PRO1184 polypeptide of SEQ ID NO:270 is capable of inducing re-differentiation of chondrocytes (Example 159), it provides no guidance or working examples as to how the skilled artisan could use a nucleic acid encoding an

inactive polypeptide variant or fragment of SEQ ID NO:270, as no functional limitation associated with the variants in the claims.

With respect to the fragment of "the extracellular domain", the specification indicates PRO1184 is a secreted protein, and does not define such domain, therefore, it is unclear whether such domain exists, and what kind of functional property it may possess. The specification provides no guidance or working example as to how to make and use such a fragment.

Further, with respect to the hybridization variants of said nucleotides, the claims read on any or all nucleotides hybridizing to SEQ ID NO:269 or to those encoding SEQ ID NO:270. It is well known in the art that hybridization will occur even under stringent conditions if there is only local identity between two molecules whose sequences might be totally divergent outside of that region. Such hybridized molecules may encode proteins capable of inducing re-differentiation of chondrocytes, yet have other distinct biological functions from those of SEQ ID NO:270. The specification does not define a specific hybridization condition for obtaining the claimed species, or working examples of any such variants, which would be within the limitations of the claims. Therefore, it would require undue experimentation in order to make the claimed invention in its full scope.

Furthermore, with respect to the small nucleotide fragment of 10 nucleotides of said hybridization variant, it may comprise 10 nucleotides which have no sequence homology to SEQ ID NO:269 or to those encoding SEQ ID NO:270. The specification provides no instruction, guidance, or working example regarding such fragments. Clearly, one of skill in the art would not know how to use such a fragment, it would require undue experimentation to practice the invention in a manner commensurate in scope with the claims.

Due to the large quantity of experimentation necessary to determine how to use the nucleic acids encoding inoperative polypeptides, and the small fragments thereof, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims which embrace a broad class of structurally diverse variants and fragments, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 119-124, 127, 128, and 132-138 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a nucleic acid having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence, SEQ ID NO:269 or a nucleic acid encoding a polypeptide of SEQ ID NO:270, hybridization variants thereof, fragments thereof, and fragments of the nucleic acid of SEQ ID NO:269, or a nucleic acid encoding the extracellular domain SEQ ID NO:270. The claims do not require that the encoded polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of nucleic acids that are defined only by sequence identity. The specification merely discloses *one* nucleic acid, SEQ ID NO:269, encoding the human PRO1184 having SEQ ID NO:270. No variants, "an extracellular domain" or other PRO1184 fragments thereof meeting the limitation of the claim were ever identified or particularly described.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved in the polypeptide encoded by the claimed nucleic acid. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at

page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of the nucleic acids. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 2701 at 2703. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In the instant application, applicants have a single polypeptide with a specific function that has not been correlated to any particular structural regions. Therefore, only isolated nucleic acid of SEQ ID NO:269, and the nucleic acid encoding the polypeptides of SEQ ID NO:270, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Rejections Over Prior Art:

The following rejections under 35 U.S.C. §§ 102 and 103 are made in view of the determination that the effective filing date for the instantly claimed invention is 30 March 2000, which is the filing date of the application of PCT/US00/08439.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 119-122 and 132-137 are rejected under 35 U.S.C. 102(b) as being anticipated by Birren et al. (Locus AC016498, GenEmbl, 3/26/00).

Birren discloses a human nucleic acid, which comprises nucleotides 4-1302 of SEQ ID NO:269 of the instant invention with 96.2% sequence similarity (see computer printout of the

search results). The cited sequence, therefore, anticipates claims 119-122 and 132-134 as being a nucleic acid having at least 80%, 85%, 90% and 95% sequence identity to a nucleic acid encoding the polypeptide of SEQ ID NO:270 (note: the coding region is nucleotides 106-531 of SEQ ID NO:269), the extracellular domain thereof, or that lacking its associated signal peptide (claims 119-122); a nucleic acid hybridizing to a nucleic acid of SEQ ID NO:270 under stringent conditions (claims 132 and 133); and a nucleic acid of the hybridization variant, which is at least 10 nucleotides in length (claim 134). Additionally, Birren teaches a vector, M13 and M77815, which was necessarily propagated in a host cell, the reference, therefore, also anticipates claims 135-137 of the instant application.

Claims 132-134 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillier et al. (Locus W16671, EST, 4/29/96).

Hillier discloses a human nucleic acid, which comprises nucleotides 663-960 of SEQ ID NO:269 of the instant invention with 89.9% sequence similarity (see computer printout of the search results). The cited sequence, therefore, anticipates claims 132-134 as being a nucleic acid hybridizing to a nucleic acid of SEQ ID NO:270 under stringent conditions (claims 132 and 133); and a nucleic acid of the hybridization variant, which is at least 10 nucleotides in length (claim 134).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claim 138 is rejected under 35 U.S.C. 103(a) as being unpatentable over Birren et al. (Locus AC016498, GenEmbl, 3/26/00), as applied to claims 119-122 and 132-137 above, and in view of Sibson et al., WO94/01548.

The teachings of the primary reference are summarized above. The primary reference does not specifically disclose a host cell of a CHO cell, an E. *coli* or a yeast cell.

Sibson discloses that it is generally useful to place a desired DNA sequence into an expression vector, host cell, and express the encoded protein (pages 8-13), and that the host cell can be prokaryotic Bacillus, eurkaryotic yeast, ... (page 9, the second paragraph).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the DNA sequence of the primary references to express the encoded polypeptide in a host cell such as a yeast cell as taught by Sibson. The person of ordinary skill in the art would have been motivated to do so in view of Sibson's suggestion that it would be desirable to do so, and reasonably would have expected success because Sibson has demonstrated such a host cell, and using a host cell such a CHO cell, an E. *coli* or a yeast cell for recombinant expression of a polypeptide of interest has been well established in the art, and conventionally practiced in the field.

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER

Dong Jiang, Ph.D.
Patent Examiner
AU1646
3/31/04